DO NOT ENTER: /C.F./ (07/27/2011)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Andreas BERGMANN	Group Art Unit 1641
Serial No.: 10/551,298	Examiner: Christine E. Foster
Filed: September 23, 2005	Confirmation No.: 3226

For: DETERMINATION OF A MIDREGIONAL PROADRENOMEDULLIN PARTIAL PEPTIDE IN BIOLOGICAL FLUIDS FOR DIAGNOSTIC PURPOSES, AND IMMUNOASSAYS FOR CARRYING OUT SUCH A DETERMINATION

RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office action dated December 23, 2010, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 11 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A method for the determination of a value for the physiological production of adrenomedullin (AM) in a human in a healthy normal or pathological state~~the mid-regional partial peptide of proadrenomedullin (mid-proAM) in a biological fluid sample from a human~~, comprising measuring ~~the level~~ in a~~said~~ biological fluid sample of said human, instead of a value for such production of AM itself, a value for production of ~~said mid-proAM~~ the mid-regional partial peptide of proadrenomedullin (mid-proAM) which consists of the sequence of SEQ ID NO: 3, wherein said measuring uses a monoclonal or polyclonal antibody which in each case is specific to said partial peptide.

2. (Previously Presented) The method according to claim 21, wherein the mid-proAM in the biological fluid is measured in an immunoassay wherein at least one antibody is employed which specifically recognizes a sequence of mid-proAM and said antibody is labeled.

3. (Previously Presented) The method according to claim 2, wherein said immunoassay using said at least one labeled antibody is an assay further employing a solid phase-bound competitor for the mid-proAM or a sandwich assay further employing at least one additional antibody which specifically binds to a different partial sequence of mid-proAM (SEQ ID NO: 3) from that bound by said at least one labeled antibody.

4. (Previously Presented) The method according to claim 21, wherein the level of circulating mid-proAM (SEQ ID NO: 3) is determined and the biological fluid is plasma or serum.

5. (Previously Presented) The method according to claim 3, wherein both antibodies bind to a region of mid-proAM which extends from the amino acid 60 to the amino acid 94 of preproadrenomedullin.

6. (Previously Presented) The method according to claim 3, wherein all said antibodies are monoclonal and/or polyclonal.

7. (Previously Presented) The method according to claim 3, wherein all said antibodies are affinity-purified polyclonal antibodies.

8. (Currently Amended) The method according to claim 3, wherein for said sandwich assay, one of the antibodies is obtained by immunization of an animal with an antigen which contains a synthetic peptide sequence which consists of~~comprises~~ the amino acids 69-86 of pre-proAM (SEQ ID NO: 4), and the other of the antibodies is obtained by immunization with an antigen which contains a synthetic peptide sequence which consists of~~comprises~~ the amino acids 83-94 of pre-proAM (SEQ ID NO: 5).

9. (Previously Presented) The method according to claim 3, wherein for said sandwich assay, one of the antibodies is labeled and the other antibody is bound to a solid phase or is not bound to a solid phase but can be subsequently bound thereto during the assay.

10. (Previously Presented) The method according to claim 3, wherein for said sandwich assay, both said at least one labeled antibody and said at least one additional antibody are present dispersed in a liquid reaction mixture and a first labeling component which is part of a labeling system based on fluorescence or chemiluminescence extinction or amplification is bound to said at least one labeled antibody, and a second labeling component of said labeling system is bound to said at

least one additional antibody so that, after binding of both antibodies to the mid-proAM to be detected, a measurable signal which permits detection of the resulting sandwich complexes is generated.

11. (Previously Presented) The method according to claim 10, wherein the labeling system comprises cryptate emission in combination with a fluorescent or chemiluminescent dye.

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Canceled)

16. (Previously Presented) The method according to claim 21, wherein said determination is carried out in the course of a multiparameter determination for diagnosis of cardiac disease in which further parameters relevant for cardiac diagnosis are also determined.

17. (Canceled)

18. (Canceled)

19. (Currently Amended) A method for the determination of a value for the physiological production of adrenomedullin (AM) in a human in a healthy normal or pathological state~~the mid-regional partial peptide of proadrenomedullin (mid-proAM) in a human~~, comprising measuring ~~the level~~ in a biological fluid sample of said human, instead of a value for such production of AM itself, a value for production of

the mid-regional partial peptide of proadrenomedullin (mid-proAM)~~said mid-proAM~~ which consists of the sequence of SEQ ID NO:3, wherein said measuring uses a monoclonal or polyclonal antibody which in each case is specific to an epitope in said partial peptide.

20. (Previously Presented) The method of claim 1 wherein said measuring is not accomplished using a competitive radioimmunoassay.

21. (Currently Amended) A method for the determination of a value for the physiological production of adrenomedullin (AM) in a human in a healthy normal or pathological state~~the mid-regional partial peptide of proadrenomedullin (mid-proAM) in a human~~, comprising measuring ~~the level~~ in a biological fluid sample of said human, instead of a value for such production of AM itself, a value for production of the mid-regional partial peptide of proadrenomedullin (mid-proAM)~~said mid-proAM~~ which consists of the sequence of SEQ ID NO:3, wherein said measuring is by immunoassay which is not a competitive radioimmunoassay.

22. (Currently Amended) A method for the determination of the value for the physiological production of adrenomedullin (AM) in a human in a healthy normal or pathological state~~the mid-regional partial peptide of proadrenomedullin (mid-proAM) in a human~~, comprising measuring ~~the level~~ in a serum or plasma sample of said human, instead of a value for such production of AM itself, a value for production of the mid-regional partial peptide of proadrenomedullin (mid-proAM)~~said mid-proAM~~ which consists of the sequence of SEQ ID NO:3, wherein said measuring is of the circulating level of said mid-proAM circulating in the blood of a patient from whom said sample is taken.

23. (Canceled)

24. (Canceled)

25. (Currently Amended) A method for the determination of a value for the physiological production of adrenomedullin (AM) in a human in a healthy normal or pathological state~~the mid-regional partial peptide of proadrenomedullin (mid-proAM)in a human~~, comprising measuring ~~the level~~ in a biological fluid sample of said human, instead of a value for such production of AM itself, a value for production of the mid-regional partial peptide of proadrenomedullin (mid-proAM)~~said mid-proAM~~ which consists of the sequence of SEQ ID NO:3, wherein said measuring is by antibody sandwich assay employing at least two antibodies specific to epitopes in said partial peptide~~sequence~~.

26. (Canceled)

27. (Canceled)

28. (Canceled)

29. (Canceled)

30. (Canceled)

31. (Previously Presented) The method of claim 19 wherein said measuring is not accomplished using a competitive radioimmunoassay.

32. (Canceled)

33. (Canceled)

34. (Canceled)

35. (Currently Amended) A method for the determination of a value for the physiological production of adrenomedullin (AM) in a human in a healthy normal or pathological state~~the mid-regional partial peptide of proadrenomedullin (mid-proAM) in a human~~, comprising measuring ~~the level~~ in a biological fluid sample of said human, instead of a value for such production of AM itself, a value for production of peptide bound by an antibody specific to the mid-regional partial peptide of proadrenomedullin (mid-proAM)~~said mid-proAM~~, wherein said mid-proAM consists of the sequence of SEQ ID NO:3.

36. (Previously Presented) A method of claim 35 wherein said measuring is by antibody sandwich assay.

37. (Previously Presented) A method of claim 35 wherein said antibody is monoclonal.

38. (Canceled)

39. (Canceled)

40. (Previously Presented) The method of claim 22 wherein said measuring is not accomplished using a competitive radioimmunoassay.

41. (Previously Presented) The method of claim 16 wherein said measuring is not accomplished using a competitive radioimmunoassay.

42. (Canceled)

43. (Canceled)

44. (Canceled)

45. (Previously Presented) A method of claim 1 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

46. (Previously Presented) A method of claim 19 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

47. (Previously Presented) A method of claim 21 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

48. (Previously Presented) A method of claim 22 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

49. (Previously Presented) A method of claim 25 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

50. (Canceled)

51. (Previously Presented) A method of claim 16 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

52. (Canceled)

53. (Canceled)

54. (Canceled)

55. (Previously Presented) A method of claim 35 wherein said measuring comprises contacting said sample with an antibody which binds to said mid-proAM forming an antibody-mid-proAM complex.

56. (Canceled)

57. (Canceled)

58. (Previously Presented) A method of claim 1 further comprising removing from a human said sample to be measured.

59. (Canceled)

60. (Previously Presented) A method of claim 21 further comprising removing from a human said sample to be measured.

61. (Previously Presented) A method of claim 22 further comprising removing from a human said sample to be measured.

62. (Previously Presented) A method of claim 25 further comprising removing from a human said sample to be measured.

63. (Previously Presented) A method of claim 16 further comprising removing from a human said sample to be measured.

64. (Canceled)

65. (Canceled)

66. (Canceled)

67. (Canceled)

68. (Previously Presented) A method of claim 35 further comprising removing from a human said sample to be measured.

69. (Canceled)

70. (Canceled)

REMARKS

Appreciation is expressed to Examiner Foster for the courteous and helpful interview of March 29, 2011. The foregoing amendments and following remarks reflect the substance of the interview.

Claim Language

The foregoing claim amendments address issues raised during the interview, the office action (pages 17 and 18) and in the advisory action of April 6, 2011. One of these involves the use of measured mid-proAM production in the body for determination of AM production in the body. (AM and ADM are used interchangeably herein to refer to adrenomedullin.) Without implying any agreement with the examiner's position that the claims must be limited in this regard, in order to expedite prosecution, corresponding language has been added. A second issue involves the preamble of the claim as discussed during the interview. Corresponding language has been added in the preamble and body indicating that the method is for the determination of production of AM. The third issue involves language related to quantitating AM.

The new language is clearly supported in the application, particularly in paragraphs 14 and 15. (Paragraph numbers refer to the published version of the application, US 2007/0212742.) See paragraph 14 regarding the object of providing a valid method "capable of giving reliable values for the physiological production of AM and/or its precursor in various pathological states . . ." As for the use of measured values of physiological production of mid-proAM as a measure of the values of physiological production of AM, instead of measured values of such AM production per se, this is also clearly supported. See, e.g., the abstract ("Method for the determination of adrenomedullin . . . in which the mid-regional partial peptide . . . is measured . . ."); paragraphs 14 and 15 ("It is therefore the Applicant's object to provide a valid method . . . capable of giving reliable values for the physiological production of AM . . . This object is achieved, according to the invention, if, instead of AM . . . a mid-regional partial peptide which contains the amino acids 42-95 of

pre-proAM (SEQ ID NO: 3) is determined . . ."); paragraph 18 ("To achieve the object of providing an assay method which reliably measures the formation of AM . . ."); and original claim 1 ("Method for the determination of adrenomedullin immunoreactivity in biological fluids for diagnostic purposes, characterized in that the mid-regional partial peptide . . . is measured."). The reference to "a healthy normal or pathological state" is included to be complete. As in any biological assay intended for diagnostics, not all patients will turn out to have a pathological condition or state; some will, of course, be in a healthy normal state. This is clear from use of the latter term (healthy normal) throughout the specification. See, e.g., paragraph 20 (line 2), paragraph 21 (line 2), paragraph 25 (line 1) and paragraph 28 (line 3), etc. See also Figures 1 and 2 referenced in these paragraphs.

In response to the examiner's advisory action, the previous reference to "levels" of the measures entities has been replaced with reference to "values." The latter term is employed in paragraph 14's description of the invention ("to provide a valid method . . . capable of giving reliable values for the physiological production of AM and/or its precursor in various physiological states . . ."). The relevant ordinary dictionary definition of "value" is: "the quantity or amount for which a symbol stands [to determine the *value* of x]." Webster's New World Dictionary, Second College Edition, page 1568 (1982) (attached). This term clearly provides the indication that "the mid-proAM level is being used as a proxy or surrogate in order to quantify the level of AM," as expressed by the examiner in the advisory action.

Should applicants have misunderstood any of the examiner's suggestions, she is urged to telephone the undersigned to expedite a resolution.

Unexpectedness

The remaining issue raised in the office action and discussed during the interview involved the fact that the stability of mid-proAM is unexpected. See the Struck Declaration.[1] It is the examiner's position that because of the nature of mid-proAM, a skilled worker would not have any particular expectation of its stability in

[1] The reference in the Struck Declaration at the end of its paragraph 3 to "Popio, et al.," should obviously be "Pio, et al."

comparison with the known instability of AM. In other words, the skilled worker would expect that the stability could be better, worse or the same. The showing of increased stability is merely one of these three "expected" possibilities. However, this rationale, it is respectfully submitted, is incorrect on at least two grounds.

The examiner's rationale does not reflect the law. The burden is on the PTO, not Applicants, to establish what would be the expectation of one of skill in the art. Here, there is only the bare allegation that, irrespective of the nature of the stability of mid-proAM, any result would be expected because it has to fall into one the three known possibilities; the same stability, higher stability or lower stability. This does not satisfy the burden on the PTO. There must be more than the mere fact that a result is "possible." Thus, the enhanced stability of mid-proAM cannot be said to be expected.

Moreover, even if the examiner's rationale were considered to be sufficient to establish that some degree of enhanced stability for mid-proAM over AM was expected, such an argument, based on the discussed alleged equivalent "possibilities," cannot realistically lead to an expectation for the very significant enhanced stability of mid-proAM. As established in the Struck Declaration with reference to Morganthaler et al., AM's notoriously poor stability includes the fact that in plasma its immunoreactivity decreases by 20 percent after storage for only 24 hours at room temperature. (Struck Declaration, page 2). In surprising contrast, Morganthaler, et al. establishes that mid-proAM is stable for at least 3 days in plasma at room temperature. See the passage bridging pages 2 and 3 of the Struck Declaration, with reference to Morganthaler, e.g., its Figure 3 and the first paragraph of its Discussion on page 1828. This surprisingly enhanced stability for mid-proAM includes stability for at least 14 days at 4 °C and for one year at -20°C.

Even if it were reasonable to expect from the fact that AM and mid-proAM are different peptides, that they would have different stabilities, nothing about these peptides of record leads a skilled worker to reasonably expect the vastly superior stability of mid-proAM. Under any reasonable scientific expectation, the significant

unexpected advantage described in the penultimate paragraph on page 3 of the Struck Declaration, is unexpected.

Further in this regard, AM and mid-proAM are peptide fragments derived from the same precursor, preproadrenomedullin. Although they are different fragments, they are still related in this sense. This is a factor indicating a relationship between the peptides. This could support the expectation that, like AM, mid-proAM could also be unstable. In any event, even if the examiner finds this fact to be irrelevant, it is certainly no less relevant than the fact on which the examiner relies, i.e., that the two peptides at issue are simply different in structure.

As for the double patenting rejections, as pointed out on the last page of the response of December 7, 2010, given that all claims are believed now to be allowable, under M.P.E.P. §804(I)(B)(1), all double patenting rejections (other than those based on 12/374,757) should be withdrawn since all of the cited applications were filed later than the above-identified application. As for 12/374,757, this is now USP 7,915,002. However, all of the claims are non-obvious over the claims of '002. Nothing in the latter claims suggests that values measured for production of mid-proAM can be used, instead of values of production of AM itself, to represent the recited production of AM. Thus, the double patenting rejection must be withdrawn.

In view of all the foregoing, it can be seen that all claims are allowable. Should the examiner have any further suggestions for an expedited allowance, she is courteously requested to telephone the undersigned.

Respectfully submitted,

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